

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

OXADIAZON

Chemical Code # 002017, Tolerance # 346

SB950 # 316

June 30, 1987

Revised 11/30/88; 10/4/89; 4/11/90; 11/29/90; 5/17/91; 5/26/95

I. DATA GAP STATUS

Combined (onco/chronic) Rat:	No data gap, possible adverse effects.
Chronic dog:	No data gap, no adverse effects.
Oncogenicity mouse:	No data gap, possible adverse effects.
Reproduction rat:	No data gap, no adverse effects.
Teratology rat:	No data gap, possible adverse effect.
Teratology rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effects.

Chromosome:	No data gap, no adverse effects.
DNA damage/Other:	No data gap, possible adverse effects.
Neurotoxicity:	Not required at this time.

Note, Toxicology one-liners are attached

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T950526

Revised by Green & Chernoff, 4/11/90; Silva, 11/29/90 & 5/17/91; Green & Silva, 5/26/95.

Record numbers through volume 346-068, listed by the Pesticide Registration Library, have been rectified with those listed in the Toxicology Summary.

II. TOXICOLOGY ONE-LINERS

COMBINED (ONCO/CHRONIC), RAT

**** 052 072694**, "Oxadiazon - 24 Month Oral Chronic Toxicity and Oncogenicity Study in Rats", (Shirasu, Y., The Institute of Environmental Toxicology, Tokyo, Japan, February 1987). Oxadiazon (95.9% pure, lot # 568.6.7.02) was fed in the diet for 104 weeks at 0, (Oriental pelleted chow MF), 3, 10, 100, and 1000 ppm to 80 Wistar (JCL:Wistar) rats/sex/group. Chronic NOEL = 100 ppm (Reduced bodyweight (4% to 11%) and increased relative liver and kidney weight was observed in 1000 ppm males. Centrilobular hepatocellular swelling and brown pigment in Kupffer's cells (lipofuscin), proximal renal tubular cells (mostly hemoglobin, some lipofuscin), and in renal cortical interstitial tissue (mostly lipofuscin) was observed in 1000 ppm males at 26, 52, 78, and 104 weeks. Hematological and clinical chemistry effects were also observed in both sexes (primarily males) throughout the study.) **Possible adverse effect indicated.** Oncogenicity NOEL = 10 ppm (An increase in benign neoplastic hepatic nodules was observed in males in a dose-related manner at \geq 100 ppm and hepatocellular carcinoma was observed in both sexes at 1000 ppm.) **Acceptable.** (H. Green & M. Silva, 10/23/90).

067 092457 This volume contains a table of the incidence of spontaneous liver tumors in JCL:Wistar Rats (for 2 year studies) from the Institute of Environmental Toxicology, Tokyo, Japan. M. Silva, 5/6/91.

024 001582-4, "Chronic toxicologic and carcinogenic study with oxadiazon in rats" (Rhodia, Inc., Hess & Clark Division, Ashland, OH #KWH 75:1, 3/15/75). Oxadiazon (CA 71300-01, 98%) in diet mix was available ad libitum to Sprague Dawley rats (40/sex/group) for 24 months. Sacrificed 5/sex/group at 12 months. Dose levels were 0, 50, 100, 500 ppm. **No adverse effects** reported. NOEL \geq 500 ppm. **Unacceptable**, not upgradeable. No justification given for dose selection, inadequate numbers of animals, missing data from ophthalmic exam. (Remsen, 8/85).

Average dose levels were approximately 2.5, 5, and 25 mg/kg/day for the respective groups. (Harnois, 6/22/87)

EPA 1-liner: Systemic NOEL >500 ppm; oncogenic NOEL >500 ppm. Supplementary.

****034 014862-4**, "Twenty-four month chronic toxicity study of oxadiazon in rats", (Nippon Institute of Environmental Toxicology, Tokyo, 7/81), Oxadiazon (18319P, 99.9% not technical grade) in diet mix at 0, 10, 100, 1000, and 3000 ppm was fed ad libitum to Fischer 344/Du crj rats (76/sex/group) for 2 years. No treatment related deaths. **Multiple adverse effects** in erythrocytes, blood chemistry, liver, kidney, eye vasculature; liver neoplasia. NOEL = 100 ppm (multiple effects). Originally found to be **acceptable**, but apparently technical grade not tested. (Remsen, 8/85). Registrant requested to justify use of purer substance (7/87 response to Rhone Poulenc petition of 11/25/86). Dose levels represented approximately 0.5, 4.8, 50.9, and 163.1 (Males); and 0.6, 5.9, 60.9, and 192.7 (Females) mg/kg/day. (Harnois, 6/30/87)

EPA 1-liner: NOEL=10 ppm (0.5 mg/kg/day); LEL= 100 ppm (5.0 mg/kg/day increase in serum protein); noted multiple effects (liver, blood chemistry, rbc's, body weight, food consumption, urine, kidney, pancreas, adrenal). NOEL(oncogenic)= 100 ppm.

CHRONIC, DOG

** 061 085654, "Oxadiazon: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks, Final Report", (Chapman, E.A., Life Science Research Limited, Suffolk, England, Report # 88/RHA116/0763, 11/29/89). Oxadiazon (94.9% pure, lot #: DA 491) was administered orally by gelatin capsule for 52 weeks (once each day, seven days per week) at 0, 5, 20, 60, or 200 mg/kg/day with 2 or 4 Beagle dogs/sex/group. NOEL = 20 mg/kg/day (Females at ≥ 20 and 1 male at 200 mg/kg/day had bradycardia. Group mean liver weight % was increased in both sexes at ≥ 60 mg/kg/day. Males at 200 mg/kg/day showed an increased mean kidney weight %. Males showed an increased ALT and PCV % and a decreased cholesterol at 200 mg/kg/day at ≥ 24 weeks. Centriacinar hepatocytic vacuolation and periacinar hepatic apoptosis was observed in both males at 200 mg/kg/day. Periacinar hepatic apoptosis was observed in 1 female and periacinar hepatic inflammation was seen in both females at 200 mg/kg/day.) **No adverse effects. Acceptable.** (H. Green & M. Silva, 10/17/90).

ONCOGENICITY, MOUSE

051, 067 072693, 092456, "Oxadiazon - 23 Month Oral Chronic Toxicity and Oncogenicity Study in Mice", (Shirasu, Y., The Institute of Environmental Toxicology, Kodaira, Tokyo, Japan, February, 1987). Oxadiazon (95.9% pure, lot no. 568.6.7.02) was fed in the diet for 98 weeks at 0 (pulverized Oriental pelleted chow MF), 3, 10, 100, and 1000 ppm to SPF ICR (JCL:ICR) mice (80/sex/group). A 52-week interim sacrifice of 10/sex/group was performed for hematology, serum chemistry, and pathology. Possible **adverse effects indicated. Chronic NOEL = 10 ppm (MCV, MCH and WBC effects were manifest as anemia in males at ≥ 100 ppm for MCV and at 1000 ppm for MCH and WBC by 98 weeks. GPT at ≥ 100 ppm and TP in males at 1000 ppm were increased by 98 weeks. ALP in both sexes and TChol in females were increased at 1000 ppm by termination. Increased mean relative liver weights in both sexes, adrenal weights in males and kidney weights in females was observed at 1000 ppm by 98 weeks. Liver lesions and hepatocellular necrosis were visible in males at ≥ 100 ppm and in females at 1000 ppm. An increase in lung lymphocytic infiltration and auricular thrombus of the heart was observed in

males at 1000 ppm.) Oncogenicity NOEL = 10 ppm (An increase in hepatocellular adenomas and carcinomas was observed in males at \geq 100 ppm and in females at 1000 ppm.) **Acceptable as an oncogenicity study only** (no ophthalmology). Previously reviewed with an adverse effect flag for lymphomas (H. Green & M. Silva, 10/23/90). Upon submission of data by the Rhone-Poulenc (067 092456) the incidence of lymphomas is not considered to be increased over historical controls. (M. Silva, 5/2/91).

067 092456 This document contains an incidence table for spontaneous tumors in JCL:ICR mice (female) from the Institute of Environmental Toxicology, Tokyo, Japan. In addition, a letter was included stating the historical controls for JCL:ICR mice were from only two studies since this strain "was banned to use in the oncogenicity study in my institution due to its high occurrence of malignant lymphoma and eventual short life span." M. Silva, 5/6/91.

****027 001585-6**, "Lifetime oncogenicity/carcinogenicity study in mice", (International Research and Development Corp. #347-008, 6/5/80). Oxadiazon (MAG 405, 95.5%) in diet mix at 0, 300, 1000, and 2000 ppm was fed to CD1 mice (60/sex/group) for 2 years. **Multiple adverse effects** in eye, blood, liver; liver neoplasia. NOEL < 300 ppm (liver changes). **Acceptable** study. (Remsen, 8/19/85). Average dose levels were approximately 50, 175 and 350 mg/kg/day for respective groups. (Harnois, 6/22/87)
EPA 1-liner: None available

001 966722--005 966726, "Oxadiazon: oncogenicity in dietary administration to mice for a period of 105 weeks", (Life Science Research, Stock, Essex, England, 82/RH0004/245, 9/17/82). Oxadiazon (BES 2253, 100%) in diet mix at 0, 100, 300, 1000 and 2000 ppm was fed to CD1 mice (70/sex/group) for 2 years. **Multiple adverse effects** in vasculature, blood, liver; liver neoplasia. NOEL < 100 ppm (liver oncogenicity). **Unacceptable**. Missing tissues for histopathology; technical grade not tested. (Remsen, 8/21/85). Doses were approximately 15, 45, 150 and 300 mg/kg/day of Oxadiazon. (Harnois, 6/22/87)
EPA 1-liner: Oncogenic NOEL < 100 ppm (LDT); (Liver neoplasms at all tested dose levels in both males and females.) CORE Grade: Guideline.

REPRODUCTION, RAT

Range-finding Study:

057 056837, "Oxadiazon: Effects of Dietary Administration Upon Reproductive Performance in the Rat, 1. Dosage Range-Finding Study.", (Tesh, J.M., et al., Life Science Research, Suffolk, England, report # 87/RHA096/434, 8/3/87). Oxadiazon (95.9% pure, batch no. DA459) was fed in the diet from 15 days prior to pairing through day 4 πρωτὶ πρῶτου at 0 (Labsure Laboratory Animal Diet No. 2, ground), 50, 100, 200, 400, and 800 ppm to 6 CD (Sprague-Dawley origin) rats/sex/group. **Adverse effect** indicated (an increase in fetal deaths at 400 ppm and an increase in resorptions at 800 ppm was observed). Reproductive NOEL = 200 ppm. Parental NOEL

= 800 ppm (No parental effects were observed at any dose.) **Supplemental** to record # 073969.
(H. Green & M. Silva, 10/24/90).

Reproduction Study:

058 073969, "Oxadiazon: Effects Upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations", (Tesh, J.M., et al., Life Science Research, Suffolk, England, report # 88/RHA097/366, 10/7/88). Oxadiazon (purity > 95.9%, batch no. DA459) was fed in the diet through two generations, 1 litter/generation (treatment began 14 weeks prior to pairing at each generation) at 0 (Labsure Laboratory Animal Diet No. 2, ground), 20, 60, and 200 ppm to 30 CD (Sprague-Dawley origin) rats/sex/group. Reproductive & Parental NOEL \geq 200 ppm (No effects were observed in parents or offspring at any dose.) **Acceptable. (H. Green & M. Silva, 10/26/90)

021 001565, "Influence of Oxadiazon (17623 R.P.) on the reproduction of the rat", (Rhone Poulenc (IFFA CREDO), 10/18/74 # IC-DREB-R 741020). Oxadiazon (RAB 2800; 98.5%) in diet mix was administered to Sprague Dawley rats in a 3-generation study (10M and 20F/group/generation) at nominal concentrations of 0, 100, 200 and 400 ppm (F0 through 1st mating) and 0, 100, 200 and 50 ppm respectively subsequently; 2 litters/generation. **Adverse effects** noted. Decreased litter size, increase in stillborns; increased post-natal mortality. NOEL = 100 ppm (fetal development, pups); and 400 ppm (parental toxicity). **Unacceptable**, not upgradeable. No stability data, no analysis of dosing preparation, change in dose levels, no histopathology on F0 or F1 parents. (Remsen, 8/15/85) Average dose was estimated as approximately 4, 9, 19 and 30 mg/kg/day for 50, 100, 200 and 400 ppm. (Harnois, 6/22/87).
EPA 1-liner: None available

TERATOGENICITY, RAT

023 001580, "Standard teratology test in albino rats (Oxadiazon, R.P. 17623)", (Biometric Testing Inc., #A-418, 10/16/72). Oxadiazon (technical, 99.1%) in corn oil was administered to pregnant rats (Wistar, ≥ 16 /group) by oral gavage at nominal levels of 0, 10, 20, 40, 60, 100, and 500 mg/kg on Days 6-15 of gestation. **Adverse effects**. Maternal body weight gain decreased, increased fetal resorption. NOEL = 60 mg/kg (maternal effect); 20 mg/kg (fetal development). **Unacceptable**, not upgradeable: missing data on litter weights, individual fetal observations, no analysis of dosing solution. (Remsen, 8/15/85)
EPA 1-liner: None available

023 001581, "Oxadiazon (17623 R.P.) teratology in the rat by oral administration", (Rhone-Poulenc, Paris, France, #16760, 2/21/73). Oxadiazon (PBA 1482, No purity) in aqueous 10% gum arabic was administered to pregnant rats (≥ 14 /group) by oral gavage at nominal levels of 0, 10, 30, 90, and 270 mg/kg on Days 5-15 of gestation. **Adverse effects**. All fetuses resorbed at 270 mg/kg; at 90 mg/kg, 3/14 dams had total fetal resorption and there was, over-all, 45% fetal resorption. NOEL ≥ 270 mg/kg (maternal toxicity); 30 mg/kg (fetal development).

Unacceptable, not upgradeable: missing data on litter weights, test substance purity; no analysis of dosing solution; too few pregnant females per group (Remsen, 8/15/85).

EPA 1-liner: None available

****046 064702**, "Oxadiazon: Teratology Study in the Rat." (Life Science Research, UK; LSR Report No. 87/RHA093/356; 8/3/87). Oxadiazon, technical grade of >90% purity, given daily by gavage at 0 (1% aqueous methylcellulose), 3, 12, or 40 mg/kg, to 20 mated Sprague-Dawley rats/group, on days 6-15 of gestation, with sacrifice on day 20. No maternal toxicity in the full study (or in a preliminary study which tested up to 80 mg/kg/day). Fetal effects were confined to the 40 mg/kg group and consisted of: 1) an increase in the group percent postimplantation loss; 2) a decrease in mean fetal weight; and 3) increased incidence of incomplete ossification. While the increased postimplantation loss was not statistically significant when compared to concurrent controls, the effect is considered real since the concurrent controls exhibited a higher-than-usual value and the preliminary study also indicates clearly an effect. Maternal NOEL > 40 mg/kg (also, no adverse effects in preliminary study up to 80 mg/kg). Possible **adverse effect**. Developmental NOEL = 12 mg/kg (increase in postimplantation loss and decreased fetal weight/incomplete ossification). **Acceptable**. Rinkus, 11/16/88.

TERATOGENICITY, RABBIT

023 001579, "Standard teratology test in albino rabbits (Oxadiazon, R.P. 17623)", (Biometric Testing Inc., #A-405, 10/16/72). Oxadiazon (technical) in corn oil was administered to pregnant New Zealand Rabbits; (10-11/group) by oral gavage at levels of 0, 100, and 500 mg/kg on Days 6-15 of gestation. **Insufficient information for assessment of reproductive effect**; NOEL = \geq 500 mg/kg (maternal). **Unacceptable**: no justification for dose selection, inadequate exposure time, no analysis of dosing preparation, inadequate number of pregnant animals. Not upgradeable. (Remsen, 8/15/85).

EPA 1-liner: None available

****047 064703** "Oxadiazon: Teratology Study in the Rabbit." (Life Science Research, UK; LSR Report No. 87/RHA095/534; 9/14/87). Oxadiazon, technical grade of >90% purity, given daily by gavage at 0 (1% aqueous methylcellulose), 20, 60, or 180 mg/kg, to 17-21 inseminated New Zealand White rabbits/group, on days 6-19 of gestation, with sacrifice on day 29. Maternal toxicity, evidenced as decreased weight gain after the start of treatment, was observed at 60 and 180 mg/kg. The 180 mg/kg group also exhibited reduced food consumption and fecal production. Fetal effects in the 180 mg/kg group included: statistically increased postimplantation loss; decreased mean fetal weight; and increased incidences of small fetuses and fetuses with bilateral hind-limb flexure, floating 13th rib/ribs, and/or asymmetric pelvis. Postimplantation loss and the incidence of floating 13th rib/ribs were also increased in the 60 and 20 mg/kg groups. Maternal NOEL = 20 mg/kg (decreased weight gain); Developmental NOEL = 20 mg/kg (Sponsor's assignment). Initially reviewed as unacceptable with no adverse health effect indicated (Rinkus, 11/29/88), the study was upgraded to **ACCEPTABLE** with submission of data in record numbers 073521 and 073522. Reviews of the supplemental and original data by G. Chernoff (9/5/89) revealed increases in percentage of resorptions and frequency of constraint-related arthrogryposis which were considered to constitute a **possible adverse developmental health effect** (G. Chernoff, 9/5/89). Supplemental information in record number 087925 failed to provide reason for changing the study status, however, the Developmental NOAEL was set equal to 60 mg/kg/day (G. Chernoff, 4/11/90).

055 073521 & 073522 Supplemental to record no. 064703, containing data on replacement rabbits, historical controls, and fetuses from females terminated prior to the scheduled time of sacrifice.

062 087925, Supplemental to record no. 064703.

GENE MUTATION ASSAYS

The data gap is filled on the basis of an acceptable mammalian cell assay and a collective evaluation of the bacterial assays.

Bacteria:

Although no one study was acceptable to fill the data gap for Oxadiazon, a composite review of the several on file shows the following:

- 1) the pure Oxadiazon was negative under these conditions for gene mutation.
- 2) some technical grades were positive in TA100 after activation by enzymes in the Aroclor-induced rat liver microsomal fraction.
- 3) several contaminants of Oxadiazon were tested and found to be negative; one (24865 R.P.) was positive in point mutation tests in bacteria after activation by the above enzymes.
- 4) one lot containing the contaminant 24865 R.P. at 0.2% was positive in point mutation tests in bacteria after activation by the above enzymes.

(Harnois, 7/1/87)

022 001568, "Microbial mutagenic study on oxadiazon--reverse mutation and host-mediated assay in S. typhimurium and E. coli." (Nissan Chemical Industries Ltd., Institute of Environmental Toxicology, Saitama-Ken, Japan, 6/4/76). 1).Plate test: Oxadiazon (99.18%) in DMSO was added at final concentrations of 0, 10, 100 and 1000 ug/plate with S9 and 0, 100, 1000 and 2500 ug/plate without S9 to duplicate cultures of E. coli (WP2 hcr-) and S. typhimurium (TA1535, TA1537, TA1538, TA98 and TA100 and G46) in the plate test. **No adverse effect** (increase in revertants) reported. **Unacceptable:** inadequate numbers of dose levels and replicates, no confirmation.

2).Host-mediated assay: Male ICR mice (6/group) received Oxadiazon (0, 1000 and 4000 mg/kg) or dimethylnitrosamine by gavage on 2 successive days. S. typhimurium (G46) was injected ip shortly after treatment, removed after 3 hrs, and cultured in selective agar. **No adverse effect** (increase in revertants) reported. **Unacceptable:** individual plate counts not provided; methods of culturing for survivors and mutants are not clearly explained; no indication that test substance (or derivatives) was in the peritoneal cavity. (Remsen, 8/85)

EPA 1-liner: None available

022 001577, "Oxadiazon (17623 R.P.) containing 90% of the active ingredient: a study of the mutagenic activity in S. typhimurium using the Ames test", (Rhone Poulenc Inc., Vitry-sur-Seine, France, #19945-E, 12/28/78). 1). Plate test: Oxadiazon (CA 76204, 90%) in DMSO was added to triplicate cultures of S. typhimurium (TA1535, TA1537, TA98, TA100) at final concentrations of 0, 125, 250, 500 and 1000 ug/plate with and without activation. **Adverse effect** (concentration-dependent increase in revertants for TA100 with activation); positive results confirmed, but negative strains not re-tested. **Unacceptable**: too few dose levels; results for negative strains not repeated; no individual plate counts; no data given for survival; no comment on solubility.

2).Spot test: Used 1000 ug in 10 ul/spot. **Insufficient information for assessment of adverse effects. Unacceptable**: no indication of diffusion through agar; insufficient numbers of concentrations and replicates. (Remsen, 8/13/85)

EPA 1-liner: 90% Oxadiazon is positive with metabolic activation in TA-100.

022 001578, "Oxadiazon (17623 R.P.) mutagenicity study in S. typhimurium using the Ames test." (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #19917-E, 12/7/78). 1). Plate test: Oxadiazon (MAG 405, 95.5%; BOS 2385, 100%) in DMSO was added to cultures of S. typhimurium (TA1535, TA1537, TA98, TA100) with and without activation. The test was performed in triplicate using appropriate controls at 0, 1, 10, 100, and 1000 ug/plate without activation and 0, 125, 250, 500 and 1000 ug/plate with and without activation. Originally (Remsen, 8/13/85), it appeared that incomplete information on solubility and lack of toxic effect would preclude an assessment. Information obtained from another study (#001571) on solubility indicated that the test was performed with maximum possible levels and that for both lots there were **no adverse effects** (clear increase in the number of revertants) reported. The study would remain **unacceptable** to fill the data gap since there were too few dose levels, results with activation were not confirmed for either lot, no individual plate counts, no data given for survival. (Harnois, Remsen; 6/30/87)

2). Spot test: Used 1000 ug in 10 ul/spot. **Insufficient information for assessment. Unacceptable:** no indication of diffusion through agar, insufficient numbers of concentrations and replicates. (Remsen, 8/13/85)

EPA 1-liner: Pure Oxadiazon is not positive in TA-98, Ta-100, TA-1535 and TA-1537 with and without activation.

022 001576, "Impurities of Oxadiazon: A study of the in vitro mutagenic activity in S. typhimurium using the Ames test", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #19959-E, 1/9/79). 1). Plate test: Four contaminants of Oxadiazon (R.P.#'s 24865, 26123, 29285 -all solids; 36227-liquid) were tested at various concentrations up to 1000 ug/plate in triplicate cultures of S. typhimurium (TA1535, TA1537, TA98 and TA100) with and without activation. **Adverse effects** (increase in revertants) with #024865 with activation in all strains; no other substances were mutagenic. 2).Spot test: Reported that #024865 at 1000 ug/spot showed **adverse effects** (increase in mutants) with activation. Both tests **unacceptable:** Oxadiazon not tested; provides supplemental information. (Remsen, 8/13/85).

EPA 1-liner: 24,855 (sic) is positive in all strains with metabolic activation. Others are not positive.

022 001575, "Impurities of Oxadiazon: A study of the in vitro mutagenic activity in S. typhimurium using the Ames test". (Rhone-Poulenc Inc., Vitry-sur-Seine, France, # 20017E, 3/79). 1.) Plate test: Six Oxadiazon contaminants in DMSO or water (39263 R.P.) were tested using triplicate cultures of S. typhimurium (TA1535, TA1537, TA98, TA100) with and without activation at concentrations up to 1000 ug/plate. **No adverse effect** (increase in revertants) reported for R.P.#'s 20088, 20531, 20930, 29284, 39263 and 39264. **Unacceptable:** Oxadiazon not tested.

2).Spot test: Same R.P.#'s tested at 1000 ug/spot. **No adverse effects** (mutant colonies) reported. **Unacceptable:** Precipitation of solids; Oxadiazon not tested; provides supplemental information. (Remsen, 8/13/85).

EPA 1-liner: Not mutagenic in TA-98, TA-100, TA-1535 and TA-1537 with and without activation.

022 001570, "Oxadiazon (17623 R.P.), Lot CA 71-300-01: Study of mutagenic activity in S. typhimurium using the Ames test", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, 7/17/80, 20688-E). Oxadiazon (CA 71-300-01, 98%) in DMSO was added at final concentrations of 0, 125, 250, 500 and 1000 ug/plate to triplicate cultures of S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100) with and without activation in the plate test. **No adverse effects** (increase in revertants) reported. **Unacceptable**. No repeat trial, no discussion of solubility. (Remsen, 8/14/85)

EPA 1-liner: 98% Oxadiazon is not positive in Salmonella.

022 001571, "Oxadiazon (17623 R.P.): Supplementary studies of mutagenesis in micro-organisms--Ames test in S. typhimurium using the Ames test", (Rhone-Poulenc Inc., Vitry-sur Seine, France, # 20673-E, 7/10/80).

1).Oxadiazon (BES 2253, 100% not technical) in DMSO at 0, 125, 250, 500 and 1000 ug/plate was tested in triplicate cultures of TA1535, TA1537, TA98, TA100, TA1538 with and without activation in the plate test. **No adverse effect** (increase in revertants) reported. **Unacceptable**. No repeat trial, not technical grade. (Remsen, 8/14/85)

2). Oxadiazon (MAG 405, 95.5%; BOS 2385, 100%) at concentrations up to 1000 ug/plate and 24865 R.P. at concentrations up to 8 ug/plate in DMSO were tested in TA1538 with and without activation to supplement previous results with the other 4 strains. **No adverse effect** (increase in revertants) reported. **Unacceptable**: No repeat trial. (Remsen, 8/14/85)

3). Oxadiazon (CA 76204, containing 90%AI and 0.2% 24865 R.P.), 24865 R.P., and mixtures of 24865 R.P with Oxadiazon Lot BOS 2385 (100%) were tested with activation in TA100, the strain previously found to give positive findings. **Adverse effects** (increase in revertants) were reported with Oxadiazon Lot CA 76204 at 2 ug/plate; with 24865 R.P. at 0.5 ug/plate; and with mixtures of Oxadiazon Lot BOS 2385 and 0.2% 24865 R.P. applied at 2 ug/plate (equivalent amount of 24865 R.P. to that in CA 76204). **Unacceptable**: No repeat trial, provides supplemental data. (Remsen, 8/14/85)

EPA 1-liner: Impure Oxadiazon (90%) and compound 24865 R.P. are positive in the Ames test with metabolic activation.

Mammalian Cells:

006 031782, "Mutagenicity evaluation of oxadiazon in the Mouse Lymphoma Assay", (Litton Bionetics Inc., Kensington, MD, # 20999, 7/82). Oxadiazon (MAG 405, 95.5%) in acetone was added to cultures of mouse lymphoma cells at final concentrations of 0 and 15.6 to 1000 ug/ml without activation or 0 and 3.91 to 62.5 ug/ml with activation. After a 4-hour exposure, the cells were washed and cultured according to standard procedures for expression of mutants. Dose-related toxicity was noted, but the original review noted that there was insufficient information for adverse effect assessment (increased revertants) because in each trial there were too few concentrations without precipitate. (Remsen, 8/12/85). Reconsideration of data from all trials indicates that there was **no adverse effect (mutant colonies) noted under these conditions and that the study can be upgraded to **acceptable**. (Harnois, Remsen; 6/17/87)

EPA 1-liner: Evaluation deferred as of March, 1982

006 031783, "Mutagenicity evaluation of Oxadiazon recrystallise in the Mouse Lymphoma Forward Mutation Assay", (Litton Bionetics Inc., Kensington, MD, #20999, 4/82). Oxadiazon (BOS 2385, 100%, not technical) in acetone was added to cultures of mouse lymphoma cells at final concentrations of 0, 31, 63, 125, 250 and 500 ug/ml without activation and 0, 16, 31, 63, 125 and 250 ug/ml with activation. After a 4-hour exposure, the cells were washed and cultured according to standard procedures for expression of mutants. The maximum soluble level was 125 ug/ml; excessive toxicity was noted at 1000 ug/ml. There was **no adverse effect** (increase in mutant colonies) reported. **Unacceptable**; insufficient number of concentrations without precipitation (Remsen, 8/12/85). Only 1 trial; the test was not performed with technical grade substance. (Harnois, 6/23/87)

EPA 1-liner: Evaluation deferred as of March, 1982.

Chromosomal Aberrations:

a. in vitro:

006 031784, "Mutagenicity evaluation of Oxadiazon in an in vitro cytogenetic assay measuring chromosome aberration frequencies in Chinese hamster ovary (CHO) cells", (Litton Bionetics, Inc., Kensington, MD, #21000, 7/82). Oxadiazon (MAG 405, 95.5%) in DMSO was added to growth stage Chinese hamster ovary cell cultures (CHO-WBI) at final concentrations of 0 and 0.416-1250 ug/ml without S9 for 7 1/2 (trial 1) or 17 3/4 (trial 2) hours; or of 0 and 1.25-125 ug/ml with S9 for 2 hrs and harvested after a 8-10 hr recovery period. A precipitate was noted in culture medium at 41.6 ug/ml; toxicity (mitotic inhibition) was noted at 125 ug/ml. **No adverse effect (increase in structural or numerical aberrations) reported. Initially reviewed as unacceptable because purity not indicated, leaving the nature of the substance unclear; data supplied (CDFA document 346-043) indicated that the substance was technical grade at 95.5% AI, allowing upgrade to **acceptable**. (Harnois, 6/23/87)

EPA 1-liner: Evaluation deferred as of March, 1983.

006 031785, "Mutagenicity evaluation of Oxadiazon recrystallise: an in vitro cytogenetic assay measuring chromosome aberration frequencies in Chinese hamster ovary cells", (Litton Bionetics Inc., Kensington, MD, #21000, 7/82). Oxadiazon (BOS 2385, 100% not technical) in DMSO was tested in CHO-WBI cells at 2-2000 ug/ml without activation, and in 2 trials at 0.7-2000 ug/ml with activation. A precipitate was noted at 200 ug/ml. **Insufficient information for assessment of adverse effects** (chromosome aberrations). since activation positive control not functioning in first trial and substance tested with activation only at insoluble levels in a repeat test. **Unacceptable.** (Remsen, 8/85)
EPA 1-liner: Evaluation deferred as of March, 1983.

b. in vivo:

022 001567, "Oxadiazon tested in the dominant lethal mutagenicity assay in mice", (Rhodia, Inc., Hess & Clark Division, Ashland, OH, 7/25/74).

Oxadiazon (CA71300-01, 98%), at nominal concentrations of 0, 100 and 500 ppm in the diet was available ad libitum to Carworth CF-1 mice (25 males/group) for 49 days. The males were mated in 2 cycles of 6 days with 2 virgin females per cycle, and the females examined 13 days after midweek of cohabitation. There was **insufficient information** for evaluation since there was no justification for dose levels, no concurrent or adequate historical control data, no purity data. The study is **unacceptable** (Remsen, 8/15/85). No diet analysis; calculated achieved dose levels were approximately 17 and 85 mg/kg/day. (Harnois, 6/23/87)

EPA 1-liner: None available

022 001574, "Oxadiazon --Micronucleus test in the mouse ", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20512-E, 2/22/80). Oxadiazon (BES 2253, 100% not technical) in 10% aqueous acacia at 0, 0.5, 1.0 and 2 g/kg was administered by oral gavage on 2 days to CD1 mice, 2/sex/dose. The animals were sacrificed 6 hrs after the second dose. This was repeated within a few weeks and data from both tests pooled for analysis. **Insufficient information for assessment of adverse effect** (presence of micronuclei). **Unacceptable:** Sampling times inadequate, animals dosed in 2 tests, no justification given for dose levels. (Remsen, 8/13/85)

EPA 1-liner: Technical is not positive

022 001573, "Oxadiazon in the micronucleus test in the mouse", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20513-E, 2/80). Oxadiazon (CA 76204, 90%) in 10% aqueous acacia at concentrations of 0, 0.5, 1 and 2 g/kg was administered by oral gavage on 2 days to CD1 mice, 2/sex/dose. The animals were sacrificed 6 hrs after the second dose. This was repeated within a few weeks and data from both tests pooled for analysis. **Insufficient information for assessment of adverse effect** (presence of micronuclei). **Unacceptable:** Sampling times inadequate, animals dosed in 2 tests, no justification given for dose levels. (Remsen, 8/13/85)

EPA 1-liner: 90% material was not positive

022 001572, "Compound 24865 R.P. in the the micronucleus test in the mouse", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20533-E, 3/13/80). A contaminant of Oxadiazon, 24865 R.P., in arachis oil at concentrations of 0, 0.5, 1 and 2 g/kg/day was administered by oral gavage on 2 days to CD1 mice, 2/sex/dose. The animals were sacrificed 6 hrs after the second dose. This was repeated within a few weeks and data from both tests pooled for analysis. Two died after 2 g/kg. Ratio of mature to polychromatic erythrocytes was increased at 2 g/kg suggesting possible toxic effect or delay in maturation. **No adverse effect** (presence of micronuclei) reported. **Unacceptable:** Insufficient numbers of animals and sampling times, animals treated on different days, a contaminant, not Oxadiazon was tested. (Remsen, 8/13/85).
EPA 1-liner: 24865 is not positive

DNA REPAIR/OTHER

The data gap is filled on the basis of an acceptable DNA repair test in mammalian cells and an acceptable transformation assay in mammalian cells. No unscheduled DNA synthesis was reported, but positive transformation findings were reported for both lots with and without activation. (Harnois, 7/1/87)

Bacteria:

022 034848, "Oxadiazon (17623 R.P.): Supplementary studies of mutagenesis in micro-organisms--induct test in E. coli.", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20673-E, 7/10/80). Oxadiazon (MAG 405, 95.5%; BOS 2385, 100%) and a contaminant, 24865 R.P., in DMSO were added to cultures of E. coli K12 GY 5057 with and without activation at concentrations of 0 and 0.1 to 500 ug/ml. **No adverse effects** (DNA change leading to induction of prophage as indicated by plaque formation) reported. **Unacceptable:** Not a standard guideline assay, but does provide useful information. (Remsen, 8/14/85)

EPA 1-liner: Not positive in the indirect (sic) test

022 034850, "Oxadiazon and impurity 24865 R.P. in supplementary studies of mutagenesis in micro-organisms--DNA-damage-repair test using E. coli", (Rhone-Poulenc Inc. Centre Nicolas Grillet, Vitry-sur-Seine, France, #20673-E, 7/10/80). Oxadiazon (MAG 450, 95.5%; BOS 2385, 100%) and a contaminant 24865 R.P. hydrochloride (no vehicle mentioned) were added with and without activation to E. coli pol A+ and pol A- cultures (1/conc.) for 2 hrs at concentrations of 0, 25, 50, 100 and 200 ug/ml then plated to measure survival. There was no adverse effect (strain-specific death indicating unrepaired damage to DNA) reported for Oxadiazon; an **adverse effect** of that type was reported for the contaminant at the highest concentration without, but not with, activation. **Unacceptable:** No information on vehicle, no justification for concentrations used, no indication of number of replicates, no description of solubility of the substances in the vehicle and in culture medium. (Remsen, 8/14/85).

EPA 1-liner: Impure Oxadiazon (90%) and compound 24865 R.P. are not positive for DNA repair.

022 034856, "Oxadiazon--supplementary studies of mutagenesis in micro-organisms: DNA damage-repair test using E. coli", (Rhone-Poulenc Inc. Vitry-sur-Seine, France, #20760, 10/8/80). Oxadiazon (CA 76204, 90%) in DMSO at final concentrations of 0, 25, 50, 100 and 200 ug/ml with and without activation was added to suspension cultures of E. coli (pol A+ and pol A-) for 2 hrs at 37 C then plated to measure survival. There was **no adverse effect** (strain-specific death indicating unrepaired damage to DNA) reported. Initially reviewed as unacceptable because of missing data on individual cultures, solubility, test description. (Remsen,

8/14/85). Additionally, since there was no toxicity observed for either strain, this appears to be a no-test situation so that a final evaluation would be insufficient information for assessment and **unacceptable**. (Harnois, 6/30/87)

EPA 1-liner: Not positive in E. coli (DNA repair)

022 034849, "Microbial mutagenic study on Oxadiazon-- Rec assay using B. subtilis", (Nissan Chemical Industries Ltd., Institute of Environmental Toxicology, Saitama-Ken, Japan, 6/76). Oxadiazon (99.18%) at concentrations of 0, 20, 100, 200, 500, 1000, 2000 ug in 0.02 ml DMSO / disk tested in B. subtilis (H17 rec+ and M45 rec-) without activation. No toxic effect was observed with either strain, indicating a no-test situation. Evaluated as having **insufficient information for assessment of adverse effect. Unacceptable**: no indication of diffusion through agar, missing data on number of replicates. (Remsen, 8/14/85)

EPA 1-liner: None available

Mammalian Cell Cultures:

****006 031786**, "Evaluation of Oxadiazon in the primary rat hepatocyte unscheduled DNA synthesis assay", (Litton Bionetics Inc., Kensington, MD., #21001, 6/82). Oxadiazon (MAG 405, 95.5%) in acetone at final concentrations of 0.5 to 100 ug/ml was added with 3H-thymidine to cultures (5/conc.) of rat hepatocytes for 18 hrs. Survival was estimated from 2 cultures and unscheduled DNA synthesis from 3 cultures. Oxadiazon precipitated at 50 ug/ml and was toxic at 25 ug/ml. **No adverse effect** (unscheduled DNA synthesis) reported. Initially reviewed as unacceptable since lack of purity data left nature of substance unclear; no solubility data. (Remsen, 8/12/85). Purity and solubility data provided (346-043 50987), allowing upgrade to **acceptable** (Harnois, Remsen 6/23/87).

EPA 1-liner: Negative at all dose levels

006 966727, "Evaluation of Oxadiazon recrystallise in the primary rat hepatocyte unscheduled DNA synthesis assay", (Litton Bionetics Inc., Kensington, MD, #20991, 6/82). Oxadiazon (BOS 2385, 100% not technical grade) in acetone at final concentrations of 1 to 1000 ug/ml was added with 3H-thymidine to cultures (5/conc.) of rat hepatocytes for 18 hrs. Survival was estimated from 2 cultures and unscheduled DNA synthesis from 3 cultures. Oxadiazon was not well dissolved at 25 ug/ml and was toxic at 50 ug/ml. **Insufficient information for evaluation of adverse effects** and **unacceptable** since there were no statistics, no individual culture data, few cultures without precipitate; also, active ingredient not defined, generalized protocol, number of replicates not clear. (Remsen, 8/12/85). Substance was not technical grade (346-043). (Harnois, Remsen; 6/23/87)

EPA 1-liner: Negative at all dose levels

****006 031791**, "Oxadiazon in the cell transformation test for carcinogenicity", (Huntingdon Research Centre, Huntingdon, England, #RNP152A/79368, 7/29/82). Oxadiazon in DMSO was added at final concentrations of 0 and 12.5-400 ug/ml with and without activation (Lot CA76204, 90%) or 0 and 25-400 ug/ml with and without activation (Lot BOS2385, 100% not technical) to duplicate suspension cultures of BHK21 C13/HRC1 cells for 4 hrs. The cells were tested for ability to grow in agar as an indicator of transformation. **adverse effects** (transformed

cells) reported for both lots with and without activation. Initially reviewed as unacceptable because of an insufficient number of plates for sampling effect per test (Remsen, 8/12/85), but reconsideration of the number of cells/plate and similar positive results for both lots both with and without activation suggests that the test would be **acceptable**. (Remsen, Harnois; 6/23/87)

EPA 1-liner: Positive test result interpretation is that Oxadiazon may have direct potential for carcinogenicity.

Yeast:

022 001569, "Oxadiazon--supplementary studies of mutagenesis in micro-organisms: DNA--gene conversion test with S. cerevisiae", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20760, 10/8/80). Oxadiazon (CA76204, 90%) dissolved in DMSO and diluted in buffer was added with and without activation at final concentrations of 0, 50, 100 and 200 ug/ml to suspension cultures of S. cerevisiae (D7) for 1 hr at 25 C. Originally reviewed as showing no adverse effect and **unacceptable** since the report did not specify number of plates used for recombination testing, DMSO not recommended solvent; unclear explanation of procedures for counting cells. (Remsen, 8/14/85). However, the use of a 1-hr incubation period does not appear to be justified, so that there would be **insufficient information for adverse effect assessment**. (Harnois 6/23/87).

EPA 1-liner: Not positive in yeast

022 034851, "Oxadiazon and impurity 24865 R.P. in supplementary studies of mutagenesis in micro-organisms: DNA gene conversion test using S. cerevisiae", (Rhone-Poulenc Inc., Vitry-sur-Seine, France, #20673-E, 7/10/80). Oxadiazon (MAG 450, 95.5%; BOS 2385, 100%) and a contaminant 24865 R.P. were dissolved in DMSO, diluted in buffer, then added to cultures of S. cerevisiae (D7) for 1 hr at 25 C at concentrations of 0, 50, 100 and 200 ug/ml. Originally reviewed as producing no adverse effect and **unacceptable** since the number of plates was not specified for recombinant studies, DMSO not recommended as a solvent, explanation of procedures for counting cells unclear. (Remsen, 8/14/85). However, the 1-hr incubation period does not appear to be justified, so that there would be **insufficient information for adverse effect assessment**. (Harnois, 6/23/87).

EPA 1-liner: Not positive in yeast

022 001566, "Genetic effects of herbicides: induction of mitotic gene conversion in S. cerevisiae", (U. Freiburg, Freiburg, W. Germany, D. Siebert and E. Lemperle, Mut. Res. 22 (1974) 111-120). Oxadiazon (Ronstar) as a commercial preparation in buffer at 1000 ppm was added to cultures of S. cerevisiae (D4) for 2 hrs at 25 C. **Insufficient information for adverse effect assessment. Unacceptable:** summary report only. (Remsen, 8/15/85).

NEUROTOXICITY

Not required at this time

ADDITIONAL INFORMATION

067 092458 Experts in carcinogenic mechanisms, Drs. Gary Williams and James Swenberg, reviewed the genetic toxicity studies and the sex chronic rodent bioassays on oxadiazon. Their reviews are contained in this volume. M. Silva, 5/6/91.

068 093000, "Studies on Morphological and Biochemical Changes in the Livers of Rats Treated for 14 Days with Oxadiazon", (S. C. Price, Robens Institute of Health and Safety, University of Surrey, Guildford, Surrey G72 5XH England, Report # RI90/0312, 1/9/91). Oxadiazon (95.6% pure) was administered by gavage to male Sprague-Dawley CD rats (10/dose) at 0 (0.5% methyl cellulose), 20, 200, and 500 mg/kg/day for 14 days. There was no NOEL (Liver weights, both absolute and relative, were significantly increased at ≥ 200 mg/kg. Discolored liver and kidneys and darkened thyroids were observed all doses. Peroxisome proliferation and indications of liver damage occurred at 500 mg/kg--only dose examined. Decreased catalase and glucose 6-phosphatase occurred at all doses. Palmitoyl CoA oxidation, palmitoyl carnitine transferase and acetyl carnitine transferase were increased at all doses. **Possible adverse effect:** Enzyme induction, indicating peroxisome proliferation occurred at all doses tested. **Supplemental** information. (H. Green & M. Silva, 5/26/95).